UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/629,074	07/31/00	CRYSTAL	R 205965

023460 HM12/0424
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EXAMINER	
PENN, M	
ART UNIT	PAPER NUMBER
1633	5

DATE MAILED: 04/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/629,074	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Claims 1-25 are pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 4, 5, 7, and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4, 5, 7, and 23, as best understood, are readable on a genus of derivatives of angiogenic proteins and osteogenic proteins, wherein none of the derivatives of the angiogenic proteins and osteogenic proteins are claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the derivatives of the proteins claimed that were angiogenic or osteogenic.

The as-filed application provides description of angiogenic proteins (e.g. $VEGF_{165}$) and osteogenic proteins (e.g. BMP-2) that can be used to enhance bone density or formation. Additionally, the specification refers to derivatives of any of these proteins, with these derivatives including those caused by point mutations, degenerate sequences, allelic variants, or genetically engineered modifications (p.4, line 3).

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential "derivatives thereof" of angiogenic proteins and osteogenic proteins containing unspecified molecular structures of molecules that are essential for the making the genus of angiogenic proteins and osteogenic proteins as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of angiogenic proteins and osteogenic proteins that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to a "derivative thereof" of angiogenic proteins and osteogenic proteins, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other derivatives of angiogenic proteins and osteogenic proteins having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not

conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of derivatives of angiogenic proteins and osteogenic proteins that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed derivatives of angiogenic and osteogenic proteins that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of derivatives of the proteins claimed that are osteogenic or angiogenic as claimed.

2. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering either 1) a vector encoding FGF or

VEGF operatively linked to a promoter or 2) a vector encoding FGF or VEGF and a second osteotropic protein each of which is operatively linked to a promoter, to a bone progenitor tissue site, a bone fracture site, an osteotemy site, a bone graft, or a bone fusion site, whereby bone density or formation is enhanced, does not reasonably provide enablement for administration of a first and second nucleic acid to a cell associated with bone, whereby bone density or formation is enhanced, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-25 of the instant application are directed towards delivery of one or more nucleic acids encoding angiogenic and/or osteogenic proteins to a region of bone. The gene therapy art at the time of the instant application, and currently, remains highly unpredictable. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the

"ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Bonadio et al. teaches that nucleic acids encoding osteotropic proteins can be delivered to bone progenitor cells located within a bone progenitor tissue site, resulting in bone growth, repair, and regeneration *in vivo*. Breitbart et al. teaches the administration of a cell that has been transfected with a vector encoding an osteotropic protein to a bone defect so that the defect can be repaired.

In the specification, a “region of bone” is defined as including the bone itself as well as the “…immediately adjoining area within the bone or in tissues surrounding it (e.g., periosteum, muscle, fascia, tendons, ligaments, etc.).” For examination purposes,

administering to at least one first cell associated with "a region of bone" is being interpreted as administered anywhere in the body because all cells in the body are "associated" with bone by being near bones and being within the same host.

The working example provided in the specification teaches that delivery of collagen sponges soaked with a solution of saline and adenoviral vector particles encoding VEGF121 or VEGF165 to a decorticated region of the spinal bones resulted in new bone formation (p.10, line 32). Decorticated refers to having the outer layer or cortex of the spine stripped or peeled away (www.harcourt.com/dictionary/; April 16, 2001; enter decorticated).

The specification does not enable delivering the nucleic acid to any "cell associated with a region of bone" as broadly claimed such that bone formation is enhanced. The specification fails to disclose methods for delivery of the nucleic acid to cells that results in enhancing bone formation other than to those in the immediate area of the bone (i.e. a decorticated region of the spinal bones), or to isolated cells in an *in vitro* setting (i.e. a bone graft). Furthermore, the specification fails to provide adequate guidance indicating that routes of delivery not to the bone, e.g. systemic, as contemplated on p.7, line 32, would result in bone growth as claimed. Although the specification teaches delivery of the nucleic acid to the bone, cells of a bone graft, it does not correlate such routes of delivery to systemic delivery or others such that bone growth would occur. For example, systemic delivery of a vector encoding an angiogenic and osteogenic protein would transduce cells of the liver and not result in targeting the protein to bone cells at a distant site. Furthermore, although the specification mentions

that viral tropism and targeting can be altered using methods known to the art (p.7, line 32), it does not teach a specific method for how this is to be accomplished, nor does it provide working examples showing that these methods target bone or enhance bone formation as claimed.

Claims 4, 5, 7, and 23 are drawn to the methods described above using a nucleic acid encoding VEGF, $VEGF_{121}$, $VEGF_{A138}$, $VEGF_{A162}$, $VEGF_{165}$, $VEGF_{182}$, $VEGF_{189}$, VEGF2, VEGF-C, FGF, a BMP, a PDGF, CTGF, angiopoiten, angiopoetin homologs, angiogenin, angiogenin-2, PlGF, BMP, TGF, LTBP, LMP-1, HBNF, GDF-5, PTH, EGF, insulin like growth factor, a growth factor receptor, a cytokine, a chemotactic factor, GMCSF, LMP, LIF, a hedgehog protein, MK, and "derivatives thereof." While the specification contemplates using derivatives thereof (p. 4, line 3), the specification does not enable one of ordinary skill in the art to make "derivatives" of any of the proteins claimed that enhance bone growth. Moreover, the specification fails to provide specifics of what the "derivatives thereof" in reference to the listed proteins consist of, or working examples that would indicate successful use in the applications claimed. For example, a derivative of VEGF could consist of a truncated or mutated form of VEGF caused by point mutation or deletion, however, this form might lack activity, thereby being nonfunctional in the applications claimed. Furthermore, a derivative could include fusion constructs comprising regions from the VEGF protein combined with regions from other proteins. While the processes of making these chimeric proteins are known in the art, the combinations of possible chimeras are endless. Moreover, functionality of these proteins, even if made, remains highly unpredictable. Lastly, a derivative could merely

be a single amino acid of the protein, which, unless shown otherwise, would not have the activity claimed. Accordingly, because of the sheer number of possible protein "derivatives" that could be encompassed by these claims and the lack of predictability of function of these proteins even if made, at the time of filing one skilled in the art would not be able to predict that delivery of a vector encoding every possible derivative of the proteins mentioned would function to promote enhancement of bone density or growth without undue experimentation.

Claim 7 includes the genus of hedgehog proteins. The specification does not enable one skilled in the are to use these proteins in a manner that would enhance bone growth as claimed. The art at the time of filing taught that administration of Indian hedgehog protein (IHP) to a fracture site resulted in increased cartilage growth. There is no indication that administration of IHP, sonic hedgehog protein, desert hedgehog protein, or any other hedgehog protein to a fracture site results in enhanced bone density or formation (Lee, M et al., 46th Annual Meeting, Orth. Res. Soc., March 12-15, 2000, p. 275; Karsenty, Genes & Development, Dec. 1, 1999, p. 3041); thus, at the time of filing one skilled in the art would not be enabled for delivery of a vector encoding any of the hedgehog proteins would function to enhance bone density or growth.

Given the guidance provided in the specification taken with the teachings in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine whether delivery of a vector encoding a derivative of the mentioned proteins operably linked to a promoter to a region of bone would result in enhancement of bone density or formation. Therefore, in view of the lack of guidance

in the specification regarding how to, the lack of correlation between, the state of the art, the examples provided and the breadth of the claims, it would have required one of skill at the time the instant invention was made undue experimentation to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what composition is being administered. While the claim states the protein is angiogenic, and angiogenic proteins are defined in the specification, the method results in enhancing bone density or formation but does not have a recitation that bone density enhancement or formation is caused by the angiogenic protein. Therefore, it cannot be determined if the nucleic acid encodes one protein that is both angiogenic and osteogenic, if the claim is directed toward a composition that is osteogenic but has an angiogenic gene, or delivering DNA encoding two sequences wherein the first is osteogenic and the second is angiogenic. In particular, claim 1 is indefinite as it relates to claim 6 because it is unclear how the limitation of claim 6 correlates to claim 1. It appears as though claim 6 encompasses delivery of nucleic acids encoding two proteins such as a VEGF and a BMP; however, it cannot be determined if the claim encompasses delivery of nucleic acids encoding two

of the same protein, or two vectors, each of which encodes the same protein that is both angiogenic and osteogenic. For example, a vector comprising two copies of the FGF gene, or two separate vectors, each encoding the FGF gene, could be encompassed by the wording of this claim. Therefore, it cannot be determined if the nucleic acid encodes a protein that is merely angiogenic or if the nucleic acid encodes a protein that is both angiogenic and osteogenic. Overall, the metes and bounds of the composition being administered are unclear because of 1) the overlap between angiogenic and osteogenic proteins and 2) the lack of clarity regarding the structure of the composition and nucleic acids being administered.

Claim 1 is further indefinite because it is unclear what applicant considers "administration to a cell associated with a region of bone." Although defined in the specification as being "within the bone ... or in other tissue adjoining the desired region," the definition is further expanded to include any cell that can be "initially away from the region and introduced into it during application of the method." Given the vagueness of this statement, the phrase encompasses administration to any tissue that is within a host. For example, administration to a blood vessel is "administration to a cell associated with a region of bone" because it is near the bone and within the same host and is equivalent to "administration to a cell associated with a region of bone" as claimed. Therefore, the metes and bounds of where the composition is being delivered cannot be determined.

Claim 7 is indefinite because a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is

considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 7 recites the broad recitation cytokines, and the claim also recites GMCSF, which is the narrower statement of the range/limitation because GMCSF is a cytokine.

Claim 17 is indefinite because it is unclear whether the first and second cell are the same type of cell or whether they are the same cell. Clarification is required.

Claim 18 is indefinite because it is unclear whether "the first and second nucleic acid are the same" means the first and second nucleic acids are two identical vectors, or if the first and second nucleic acids are in the same vector.

Claims 23-25 recite the limitation "...the bone graft..." in claim 19. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-4, 6, 7, 17, 18, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Bonadio (Bonadio et al., US Patent 5,942,496, Aug. 24, 1999).

Bonadio teaches administering a composition comprising a matrix and an adenoviral vector encoding FGF to a bone progenitor tissue site of an animal such that bone progenitor cells express the proteins and bone tissue growth occurs (claims 23, 26, 34, 40; claims 54, etc.). Bonadio also teaches bone progenitor cells, including stem cells, macrophages, fibroblasts, vascular cells, osteoblasts, chondroblasts, or osteoclasts, that have been transfected with a nucleic acid encoding FGF delivered to them *ex vivo* and administration of the cells to the bone progenitor site such that bone tissue growth occurs (col. 5, line 24; col. 11, line 26). The bone progenitor site is a cell "associated with a region of bone" (claim 1) because the bone progenitor site is a bone fracture site and osteotomy gap and is part of the bone (col. 26, line 12; col. 29, line 42; col. 47, line 7). FGF is also angiogenic as claimed (claim 1) because FGF inherently induces vasculogenesis.

Administering at least one of the nucleic acids encoding an angiogenic protein to at least one cell in vivo in the region of bone (claim 2) is anticipated by Bonadio

because Bonadio teaches administration of at least one nucleic acid encoding FGF to a bone progenitor site in a host.

The limitation of administering a first nucleic acid encoding an angiogenic protein and second nucleic acid encoding an osteogenic protein (claim 6) is anticipated by Bonadio because Bonadio teaches administration of more than one nucleic acid encoding VEGF. Two copies of a vector encoding either FGF are equivalent to the first and second nucleic acid claimed because FGF is both angiogenic and osteogenic.

Administering a first nucleic acid to a first cell and second nucleic acid to a second cell (claim 6) is anticipated by Bonadio because at least two cells inherently express FGF and because the vector inherently comes into contact with at least two bone cells when delivered to a bone progenitor site.

The limitation that a first and second cell are the same (claim 17) is anticipated by Bonadio because the cells at the bone defect are the same in that they are bone cells. The limitation of a first and second nucleic acid that are the same (claim 18) is anticipated by Bonadio because multiple copies of the same vector are introduced into the bone progenitor site.

The bone graft of claims 22 and 23 is equivalent to the transfected cells because they are grafted into the bone progenitor site. The first and second nucleic acid are equivalent to two cells each with a vector encoding FGF, which both is angiogenic and osteogenic.

5. Claims 1, 3, 4, 6, 7, 17, 18, 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Breitbart et al. (U.S. Patent 6,077,987, June 20, 2000).

Breitbart teaches transfecting chondrocytes, mesenchymal cells, or fibroblasts with a vector encoding FGF or VEGF *in vitro*, administering the cells to cranial bone defects and enhancing bone growth at the defect site (col. 3, line 52; claims 1,5).

Administering the cells to the bone defect is equivalent to exposing the cell *in vivo* in the region of bone (claim 2) because the cells of the bone defect *in vivo* are exposed to the vector. Transfecting cells *in vitro* and administering the cells to the bone defect in an animal is equivalent to exposing the cells to the vector *ex vivo* and delivering the cells to the bone defect *in vivo* (claim 3). FGF and VEGF are also angiogenic because inherently induce vasculogenesis.

The limitation of administering a first nucleic acid encoding an angiogenic protein and second nucleic acid encoding an osteogenic protein (claim 6) is anticipated by Breitbart because Breitbart teaches administration of more than one vector encoding FGF or VEGF. Two copies of a vector encoding FGF or VEGF are equivalent to the first and second nucleic acid claimed because FGF and VEGF are both angiogenic and osteogenic.

Administering a first nucleic acid to a first cell and second nucleic acid to a second cell (claim 6) is anticipated by Breitbart because at least two cells inherently express FGF or VEGF and because the vector inherently comes into contact with at least two bone cells when delivered to the site of the bone defect.

The limitation of a first and second cell are the same (claim 17) is anticipated by Breitbart because the cells at the bone defect are the same in that they are bone cells. The limitation of a first and second nucleic acid that are the same (claim 18) is anticipated by Breitbart because multiple copies of the same vector are introduced into the bone defect.

The bone graft of claim 22 is equivalent to the transfected cells of Breitbart because they are grafted into the bone defect. The first and second nucleic acid are equivalent to two cells each with a vector encoding FGF or VEGF which are both angiogenic and osteogenic.

The graft is an allograft (claim 24) because the cells are isolated from New Zealand white rabbits and grafted into other New Zealand white rabbits (col. 13, lines 41-55; col. 1, line 67).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 6, 8-10, 17-23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonadio et al. (Bonadio et al., US Patent 5,942,496, Aug. 24, 1999).

Bonadio teaches administration of a nucleic acid encoding FGF and a second osteotropic protein to bone progenitor cells. Bonadio further teaches administering a

composition comprising a matrix and a nucleic acid encoding both a PTH protein and a BMP protein to a bone progenitor tissue site of an animal such that the bone progenitor cells express the proteins and bone tissue growth occurs (claims 38, 39). Bonadio does not specifically teach delivery of the combination of FGF with either TGF-β1 or BMP-2, however, Bonadio does teach that the second protein is BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, LTBP, PTH, EGF, PDGF, GM-CSF, LIF, TGF-β1, or FGF (claims 34 and 42). Moreover, Bonadio teaches administration of several osteotropic genes in combinations designed to stimulate bone growth (col. 9, line 16). One of ordinary skill in the art would be motivated to use a nucleic acid encoding FGF and at least one of either BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, LTBP, PTH, EGF, PDGF, GM-CSF, LIF, TGF-β1, or FGF to enhance bone growth or repair. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

7. Claims 1, 6, 13, 14, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breitbart et al. (Breitbart et al. U.S. Patent 6,077,987, June 20, 2000) in view of Bonadio (Bonadio et al., US Patent 5,942,496, Aug. 24, 1999).

Breitbart teaches transfecting a cell with a vector encoding VEGF, administering the cells to cranial bone defects and repairing the bone defect (col. 3, line 52; claims 1,5). Breitbart does not teach delivery of a vector encoding both VEGF and BMP-2 or TGF-β1. Bonadio teaches administration of a nucleic acid encoding the angiogenic protein FGF and a second osteotropic protein to bone progenitor cells, but not VEGF and a second osteotropic protein. However, Bonadio teaches administration of several osteotropic genes in combinations designed to stimulate bone growth (col. 9, line 16).

In view of the teachings of Breitbart and Bonadio, one of ordinary skill in the art would be motivated to use a nucleic acid encoding VEGF and at least one of either BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, LTBP, PTH, EGF, PDGF, GM-CSF, LIF, TGF-β1, or FGF to a region of bone to enhance bone growth. All of these proteins are osteogenic in nature, therefore because of the numerous different cell types involved in bone growth and repair, and the knowledge that these different proteins elicit specific reactions from these cell types during bone growth or repair, in combining them it would be expected that an enhanced effect on bone growth or repair would be seen over the administration of only a single nucleic acid encoding one of these proteins. Additionally, if claim 18 required two copies of the same osteotropic gene in one vector construct, it would have been obvious to put two copies of the VEGF gene in the construct to enhance expression levels of the gene. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

8. Claims 1, 6, 7, 11, 12, 15, 16, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonadio et al. (Bonadio et al., US Patent 5,942,496, Aug. 24, 1999) and Breitbart et al. (Breitbart et al. U.S. Patent 6,077,987, June 20, 2000) as applied to claims 1, 6, 13, 14, and 18 above, further in view of Colley (Colley, WO 9953943 published Oct. 28, 1999).

The combined teachings of Breitbart and Bonadio teach administration of a vector encoding VEGF and a second osteotropic protein to a bone defect to enhance

bone growth. The combined teachings of Breitbart and Bonadio do not teach a vector encoding midkine (MK) or pleiotrophin (also known in the art as HBNF). However, Colley teaches administering a vector encoding midkine or pleiotrophin to a bone defect to enhance bone growth. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the osteogenic proteins taught by Bonadio or Breitbart with the osteogenic proteins MK or HBNF to enhance bone growth. All of these proteins are osteogenic in nature and because of the numerous different cell types involved in bone growth and repair, and the knowledge that these different proteins elicit specific reactions from these cell types during bone growth or repair, in combining them it would be expected that an enhanced effect on bone growth or formation would be seen over the administration of only a single nucleic acid encoding one of these proteins. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonadio et al. (Bonadio et al., US Patent 5,942,496, Aug. 24, 1999) and Breitbart et al. (Breitbart et al. U.S. Patent 6,077,987, June 20, 2000) as applied to claims 1, 6, 13, 14, and 18 above, further in view of Ferrara et al. (Ferrara et al., Endocrine Reviews, Feb. 1992, p. 18-32) or Neufeld et al. (Neufeld et al., FASEB, Jan. 1999,.p. 9-22).

The combined teachings of Bonadio and Breitbart teach administration of a vector encoding VEGF and a second osteotropic protein to a bone defect to enhance bone growth. The combined teachings of Bonadio and Breitbart do not teach using the

$VEGF_{121}$ or $VEGF_{165}$ isoforms of VEGF. However, Ferrara et al. teaches that VEGF121 and VEGF165 promote angiogenesis as determined by promoting endothelial cell growth (p.21,22). Neufeld et al. also teaches that $VEGF_{121}$ and $VEGF_{165}$ induce endothelial cell proliferation and in vivo angiogenesis (p.14). It would have been obvious to one skilled in the art at the time the invention was made to administer a vector encoding VEGF to a bone defect to enhance bone growth as taught by Bonadio and Breitbart, using the $VEGF_{121}$ or $VEGF_{165}$ isoforms taught by Ferrara or Neufeld. One of ordinary skill in the art would have been motivated to use a vector encoding $VEGF_{121}$ or $VEGF_{165}$ because they are the most efficiently secreted isoforms of VEGF (Ferrara et al., p.22, column 2, first and second paragraphs; Neufeld et al., p. 14, column 2, end of paragraph); thus they would exert the desired effect of inducing endothelial cell growth in a bone defect by transduction of either endothelial cells or non-endothelial cells in the bone defect, instead of relying on specific targeting of endothelial cells in the bone defect. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

No claims are allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael G. Penn who can normally be reached on Monday through Friday from 8:00 am to 4:30 p.m. at (703) 308-2454.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, who can normally be reached on Monday through Friday from 9:00 am to 5:30 p.m. at (703) 305-3015.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

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